Vaccine trials in melanoma – time for reflection

Alexander Eggermont

The disappointing results of the large, randomised controlled trials showing no benefit of vaccines in patients with advanced and metastatic melanoma call for a reassessment of the development of therapeutic vaccines and the importance of better immune monitoring methodology, such as adoptive T-cell therapy with lymphodepletion.

Melanoma is considered one of the most immunogenic solid tumours and the ideal candidate against which to develop various immunotherapeutic approaches. This is based on observations of spontaneous remissions, the prognostic importance of lymphocytic infiltration in primary melanomas and responses to a variety of cytokines. Antibodies, cytokines, adoptive transfer of effector cells, immunologic preconditioning of the patient and various vaccine approaches are all of interest in the development of immunotherapeutic regimens. Overcoming various immunosuppressive conditions at the tumour site and breaking immune tolerance are probably key for further progress in this field. The complexity of orchestrating immune responses is such that success has been rather limited.

The development of an effective therapeutic vaccine for metastatic melanoma continues to be the elusive 'holy grail' in a disease where other systemic treatment approaches continue to fail. The notable exceptions at present are the adoptive immunotherapy regimens tested at the National Cancer Institute (NCI) Surgery Branch in patients with metastatic disease.[1] Apart from that endeavour, however, we cannot escape the very disappointing results of large, randomised controlled trials, both in patients with stage IV melanomas and in the adjuvant setting for stage II, stage III and resected stage IV disease. This situation calls for a moment of reflection.[2]

Rosenberg and co-workers stated that despite great advances in the field of tumour immunology in the past decades, optimism about the clinical application of currently available cancer vaccines is based more on surrogate endpoints than on the observation of clinical tumour regressions.[3] They questioned the validity of this optimism, as well as the robustness of surrogate immunomonitoring endpoints. Cancer vaccine trials in 440 patients, conducted at the NCI Surgery Branch, had an overall objective response rate of only 2.6%. This result is comparable to the 4.0% response rate reported in 40 studies that involved 756 patients.[3] It

nature REVIEWS CLINICAL ONCOLOGY

This article was first published in *Nature Reviews Clinical Oncology* 2009 vol. 6 no.5, and is published with permission. doi:10.1038/nrclinonc.2009.42, www.nature.com/nrclinonc

is clear that with these very low response rates, surrogate endpoints for tumour regression are virtually impossible to identify. Smith and colleagues, of the NCI Surgery Branch, reported that in 305 patients in whom peptide-vaccines were combined with high-dose interleukin 2 (IL-2), the results were almost identical to those obtained in 379 patients treated with IL-2 alone.[4] Only the combination of IL-2 with the immunogenic peptide gp100:209-217(210M) was associated with an increased response rate, in their experience. Sosman and colleagues, however, did not observe such an increase for this peptide in three phase II trials involving 131 patients, and could only confirm the activity of high-dose IL-2.[5]

The disappointing results in patients with advanced stage IV disease are often played down by arguments that immunosuppressed patients with stage IV disease are unsuitable for vaccine development studies, and that vaccines can probably only be successfully developed in immunocompetent patients after full resection of their tumour(s) (that is, in the adjuvant setting). However, it is precisely in this setting that large trials of adjuvant vaccines in patients with stage II–IV resected tumours have failed or, even worse, have given an indication of being potentially detrimental.

An allogeneic cancer vaccine (Canvaxin), developed from three cell lines, was used in clinical trial testing. In two large, randomised trials, 1,166 patients with stage III melanoma and 496 patients with resected stage IV melanoma were randomly allocated to receive Canvaxin plus Bacillus Calmette–Guérin (BCG) or placebo plus BCG after surgery. Both trials were closed prematurely on the advice of the independent data monitoring committee. There was a survival disadvantage in patients receiving Canvaxin treatment in both studies. Median survival in the stage III study had not been reached, but the five-year survival was 59% for those who received Canvaxin, and 68% for untreated patients. In the stage IV study, median survival was 32 months for patients treated with Canvaxin and 39 months for patients who received placebo, with respective five-year survival rates of 40% and 45%. The large phase III EORTC 18961 trial of adjuvant ganglioside vaccine GMK in 1,314 patients with stage II melanoma was stopped early by the independent data monitoring committee because of inferior survival in the vaccine treatment arm.[6] This difference in survival at the second interim analysis was quite similar to that observed in the second interim analysis of the ECOG1694 trial, in which 880 patients with stage IIB–III disease were randomly allocated to high-dose interferon (IFN) therapy or the GMK vaccine.[7] This trial is difficult to interpret with respect to the potential detrimental effect observed.[2] Clearly the results of these large adjuvant trials are a substantial setback to the development of a vaccination strategy in melanoma.

Results from large, randomised trials in stage IV melanoma have not indicated a turn for the better. In vaccine development, optimisation of antigen presentation with dendritic cells has increased our knowledge of the mechanisms involved, but until now this has not resulted in clear advances in the clinical situation. The first large, randomised phase III trial comparing autologous peptide-pulsed dendritic cell vaccination with dacarbazine in stage IV melanoma was closed after 108 patients had been treated. This decision was made on the basis of the interim analysis, which indicated that there were no significant differences in the response rate or overall survival between the two treatment arms.[8] As evaluated in a systematic review in 2008, no vaccines with proven clinical efficacy are available.

Immunosuppression mechanisms at the tumour site, and the critically important role of the tumour microenvironment, are now better understood. T-cell activation will only take place when an antigen is presented by a major histocompatibility complex molecule and a co-stimulatory molecule, B7.1 or B7.2. Binding of B7 molecules to CD28 then leads to T-cell activation, which in turn upregulates CTLA4, which competes for binding to B7, resulting in inhibition of T-cell receptor signalling, IL-2 gene transcription and T-cell proliferation. CTLA4 thus has a critical inhibitory role in T-cell control, and blocking this function can be a crucial step in augmenting and maintaining cytotoxic T-cell responses, which is so desperately needed in cancer immunotherapy. The two monoclonal antibodies to CTLA4, ipilimumab and tremelimumab, can break self tolerance, and thus mediate antitumour effects; however, this can result in autoimmunity in some tissues (also called immune-related adverse events). The antitumour effect of anti-CTLA4 antibody administration seems to be a result of increased T-cell activation, rather than inhibition or depletion of T-regulatory cells. Strikingly, in various patients with stage IV disease, slowly developing, long-lasting complete remissions have now been observed. These observations have been made both in melanoma patients with extensive metastatic disease and patients who have failed various previous treatments.

Another monoclonal antibody that has been developed acts against the programmed death 1 receptor (PD-1R), the ligand of which (PD-1L) can be directly expressed on melanoma cells. PD-1R is a part of the B7:CD28 family of co-stimulatory molecules that regulate T-cell activation and tolerance, and thus anti-PD-1R can have a role in breaking tolerance.[9] The antibodies, anti-OX44 and anti-1-4BB, which have an agonistic action on T-cell activation, and the anti-CD25 antibody, which targets vmx

T-regulatory cells that constitutionally overexpress CD25, are examples of other potential candidates to be combined with vaccines. It has been demonstrated that combinations of these antibodies can significantly optimise T-cell responses; thus, we are probably witnessing an emerging field of immunomodulation that holds great promise.[10] These antibodies might be crucial to the successful development of vaccines in the future.

Rosenberg's group reported on the very impressive response rates in 93 patients with metastatic melanoma who received adoptive T-infiltrating tumour-lymphocyte therapy in combination with high-dose IL-2 after myeloablative conditioning therapy with fludarabine and cyclophosphamide with or without total body irradiation. Lymphodepletion is one of the hallmarks of this innovative approach, and seems to have a crucial role in its success. Immunosuppressive lymphocyte populations in patients with advanced metastatic melanoma (that is, lymphocytes that also compete for IL-2) need to be eliminated to allow for an effective adoptive transfer of tumour-infiltrating T-cells, which can then thrive on the concomitantly administered IL-2. Competition for IL-2 by other lymphocyte populations has been reported to be able to abrogate efficacy of adoptive immune therapy.[11] The current approach that reported 50%–72% response rates, with complete response rates of 9%–16% depending on the combination with degree of total body irradiation, is of great importance. It not only demonstrates that immunotherapy has a future, but it also demonstrates that concepts such as lymphodepletion might be important for vaccine development strategies.[12]

It is time to pause and reassess the development of therapeutic melanoma vaccines. The potentially detrimental effects that have been observed in adjuvant trials should lead to a cautious approach, and to the development of better immune monitoring methodology. Vaccine development in stage IV disease might require the introduction of some of the new potent and innovative immunomodulatory antibodies that considerably enhance and maintain T-cell activation. Moreover, we should be greatly encouraged by the success of the adoptive T-cell therapy with lymphodepletion approaches conducted at the NCI Surgery Branch. This approach may well contain crucial elements that could lead to eventually successful therapeutic vaccination strategies.

Details of the references cited in this article can be accessed at www.cancerworld.org/magazine

Author affiliation: Department of Surgical Oncology, Daniel den Hoed Cancer Centre, Erasmus University MC, Rotterdam, The Netherlands
Competing interests: The author has declared he is a consultant for the Schering–Plough Research Institute and receives research support from this organisation